Reviewer's report

Title: Antiviral Treatment Perspective against Borna disease virus 1 infection in Major Depression: A Double-Blind Placebo-Controlled Randomized Clinical Trial

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Reviewer: Tomoyuki Honda

Reviewer's report:

Dietrich et al. demonstrated that amantadine had an antidepressant effect over placebo in BDV-1-infected patients with MD or BD by a double-blinded placebo-controlled randomized clinical trial with a cross-over period. Also, they confirmed the safety of amantadine. Then, they found that the amounts of pre-treatment antibodies were predictive of clinical improvement by amantadine. Finally, they demonstrated anti-BDV-1 effects using de novo infection system. The study seemed to demonstrate the antidepressant effect of amantadine. However, the link between BDV-1 infection and depression was obscure. There are some suggestions to improve this study.

The most major concern of this study is that they could not conclude amantadine, which is known to have an antidepressant effect, exhibited their effect through BDV-1 suppression. Although the amounts of antibodies correlated with clinical improvement, it is just a correlation and not a causative relationship. To evaluate more, the study using known anti-BDV-1 antivirals without an antidepressant effect, such as ribavirin and T-705 (favipiravir), could be considered. Please discuss this point.

Another concern is they used BDV-1 acute infection model to evaluate in vitro efficacy studies of amantadine. However, in MD or BD patients, the virus is expected to have established a persistent infection. Therefore, it is better to analyze the reduction of BDV-1 load by amantadine using BDV-1 persistently infected cells.

Lines 410-413. This is difficult to understand. Please show the plot graph for these data and indicate the amantadine and placebo groups. Did they detect this correlation only in the amantadine group but not in the placebo group? How were the results in period II?

Lines 566-570. Why pre-treatment BDV-1 values, but not BDV-1 reduction, correlated with clinical outcomes. If BDV-1 reduction is an important mechanism for the antidepressant effect of amantadine, it should correlate. They should discuss this point.

Line 70. What is "DALYs"? Please indicate.
Lines 249-251. They should clarify when they started to add amantadine.

Lines 251. It is not clear how did they measure virus titer. Did they evaluate the titer in the culture medium of OL cells or the cell lysates? What did they mean by "as above"?

Line 442. What did they mean by "additive BDV infection values"? Please indicate.

Line 641-642. This is too much. They have just shown the correlation.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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